

**REMARKS***Status of the Claims*

Claims 17, 21-24, 26, 28, 29, 31, 33, 38, and 41-44 are in the application.

Claims 17, 21-24, 26, 28, 29, 31, 33, 38, and 41-44 have been rejected.

Claims 17 and 41 have been amended. Claims 43-44 are hereby canceled.

The amendment is supported by the specification in general and, specifically, is the result of taking the limitations of canceled claim 43 and incorporating same into independent claim 17. The addition of “synthetic” in claims 17 and 41 is disclosed in, among other sections, paragraph 0026 of the specification. No new matter has been added.

Upon entry of this amendment, claims 17, 21-24, 26, 28, 29, 31, 33, 38, and 41-42 will be pending.

**I. Rejections under §102(b)**

Claims 17, 21, 31, 33, 38 and 42 stand rejected under §102(b) over Alila et al. As amended herein, the Alila reference fails to anticipate the claimed invention.

In an effort to progress the prosecution of this application, Applicants have amended the claims to incorporate the electroporation step into the independent claim 17. Furthermore, to more clearly define the claimed invention, the claims have been amended to add “synthetic” to limit the myogenic promoter element. The Alila reference fails to describe all elements of the claimed invention and, thus, is not anticipatory.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP § 2131. Alila fails to meet this standard of anticipation.

The Patent Office incorrectly characterizes the teachings of the Alila reference, which with the aid of improper hindsight can lead to an improper anticipation analysis. While the Alila reference discusses IGF-I and its possible role in nerve and skeletal muscle development, the

product use for in vivo studies (on male fisher 344 rats) was a DNA plasmid (pIG0100 or pIG0552) with hIGF-I expression cassette formulated with PVP that was injected into exposed muscle (see p.1787 col. 1 and p.1789, col.2). GAP-43 was detected by immunostaining as a marker for motor neuron sprouting (see Abstract) – not angiogenesis. Furthermore, of these 2 products tested in vivo in rats, one (pIG0100) was determined not to show positive GAP-43, and this was explained to be the result of inefficient secretion (see p.1793, col.2). Without impermissible hindsight, using the Applicant's invention as a roadmap, it is difficult to see how the Alila reference, which uses a PVP formulation and fails to use electroporation and a synthetic myogenic promoter, and only shows positive marker GAP-43 for one of two plasmids – not angiogenesis - can anticipate the claimed invention.

For added emphasis to Applicants' rebuttal, the Alila reference makes a number of statements, including that described in above-paragraph, that shows the difficulty and unpredictability of IGF-I therapy for neuronal development due to ineffective expression. There is nothing disclosed in Alila regarding electroporation or the formulation and promoter used in the claimed invention. Thus it is difficult for one of ordinary skill to make the conclusion that such differences would or would not result in the same expression level-concerns. Therefore, the claimed invention is not anticipated by the Alila reference.

Additionally, since the product and method used in the Alila reference is not the same as the claimed invention, the inherent anticipation rationale for defeating patentability is improper. The standard for showing an inherent disclosure in the prior art is suggested in MPEP § 2112, "To establish inherency, the extrinsic evidence '**must make clear that the missing descriptive matter is necessarily present**' in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" (emphasis added). The Patent Office has failed to meet such a standard for establishing an inherent disclosure in the Alila reference because as shown in Alila, a product failed to show the marker, and thus even in the Patent Office's inherency theory did not inherently lead to angiogenesis.

Accordingly, it is respectfully requested that this rejection be withdrawn.

## II. Rejections under §103

A. Claims 22 and 23 have been rejected under 35 U.S.C. 103(a) as unpatentable over Alila, *et. al.*, in view of van Deuterkom, *et. al.* (hereinafter “Deuterkom”). Applicants respectfully traverse.

Applicants maintain that the teachings of Alila and Deuterkom cannot be combined to render obvious the claimed invention because the combination fails to teach the claimed invention. In addition, Applicants assert that one of ordinary skill in the art would not combine the teachings of the claimed invention because one of ordinary skill in the art would not recognize the benefit of the combination of references.

Alila is discussed above, and the same arguments are applicable here.

It is asserted that it would have been obvious for one of ordinary skill in the art to modify the method of Alil to mix the isolated nucleic acid expression construct with a transfection – facilitation system, such a liposome with a reasonable chance of success. (Office Action, page 7). A statement that modifications of the prior art would have been “well within the ordinary skill of the art a the time the invention was made because the references teach that all aspects of the claims were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the references. *Ex parte Levengood*, 28 USPQ 2d 1300 (BPAI, 1993). The Office has failed to provide an objective reason to combine the references.

Deuterkom discloses methods of improving transduction of viral vectors. However, Deuterkom does not teach, mention or suggest methods of stimulating angiogenesis. In addition, Deuterkom does not teach a subject with a muscle injury as required by the claims. Without impermissible hindsight, one of ordinary skill would not be motivated to combine these references.

The Patent Office on Page 6 of the Office Action improperly supports the obviousness rejection when stating the rule of same chemical products having same properties. The Patent Office is reminded that Alila used GAP-43 as a marker for motor neuron sprouting. There is nothing taught therein to say that every time GAP-43 appears that angiogenesis is being

stimulated. Simply knowing or having IGF-1 does not necessarily result in “stimulating angiogenesis.”

Neither Alila nor Deuterkom reference teaches or suggests stimulating angiogenesis, or stimulating angiogenesis in a subject with a muscle injury. One of ordinary skill in the art would not be motivated to modify a reference disclosing nerve regeneration with a reference disclosing liposomes to arrive at a method of stimulating angiogenesis using the claimed nucleic acid construct in combination with a transfection-facilitating system before delivering the isolated nucleic acid expression construct into the muscle tissue of the injured muscle of the subject. The Office has therefore not established a *prima facie* case of obviousness.

The Office has failed to properly establish a *prima facie* case of obviousness under 35 U.S.C. §103(a). Applicants respectfully request that the rejection be withdrawn.

B. Claims 17, 24, 28, 29, 41, 43, and 44 stand rejected under 35 U.S.C. § 103(a) over Alila in view of Draghia-Akli, Fewell, and Isner. Applicants respectfully traverse.

Applicants maintain that the teachings of Alil, Draghia-Akli, Fewell, and Isner cannot be combined to arrive at the claimed invention because the combination of the teachings does not yield the claimed invention. Applicants assert that one of ordinary skill in the art would not combine the teachings because one of ordinary skill in the art would not recognize the benefit of the combination of references.

Again, applying the arguments of the above-section directed to the 102 and 103 rejections, the Alila reference fails to disclose the claimed invention directed towards methods of stimulating angiogenesis with the provided nucleic acid expression constructs. Alila fails to disclose administration of nucleic acid constructs with muscle injury. The secondary references cited herein fail to make up for the deficiencies of the Alila reference. As a result, these cited references, alone or in combination, fail to render the claimed invention obvious.

Accordingly, it is respectfully requested that this rejection be withdrawn.

### ***Conclusion***

In conclusion, the Applicants submit that all pending claims are in condition for allowance and request an early indication of the same. Should the Examiner have any questions that may be addressed through a teleconference, the Examiner is invited to contact the undersigned attorney.

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Account No. 50-4992.

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